Prognostic Impact of Central Sleep Apnea in Patients With Heart Failure

WOLFRAM GRIMM, MD,[1] ANTONINA SOSNOVSKAYA, MD,[1] NINA TIMMESFELD, PhD,[2] OLAF HILDEBRANDT, MSc,[3] AND ULRICH KOEHLER, MD[3]

Marburg, Germany

ABSTRACT

Background: Central sleep apnea (CSA) is common in patients with heart failure (HF). Earlier studies investigating the influence of CSA on mortality in HF patients, however, have yielded contradictory results.

Methods and Results: In a prospective study involving 267 patients with left ventricular (LV) ejection fractions ≤50%, we performed polysomnography and compared heart transplant−free survival rates between patients with no or mild CSA (apnea-hypopnea index [AHI] ≤15/h) and those with moderate CSA (AHI 15.1−30/h) or severe CSA (AHI >30/h). During 43 ± 18 months' mean follow-up, 67 patients (25%) died and 4 patients (1%) underwent heart transplantation. Multivariate Cox analysis identified age, male sex, chronic kidney disease, and decreased LV ejection fraction, but not moderate CSA or severe CSA, as predictors of transplant-free survival.

Conclusions: In patients with stable HF, moderate CSA as well as severe CSA do not appear to predict transplant-free survival independently from confounding factors. (*J Cardiac Fail 2015;21:126−133*)

Key Words: Central sleep apnea, heart failure, transplant-free survival, polysomnography.

Sleep-disordered breathing is a highly prevalent but underdiagnosed finding in patients with heart failure (HF). Although the frequency of obstructive sleep apnea (OSA) in CHF patients is similar to or moderately higher than that observed in the general population, central sleep apnea (CSA) has been observed in 21%−82% of patients with HF.[1−12] In patients with HF, both prevalence and severity of CSA have been associated with HF severity with increased neurohumoral activation, elevated B-type natriuretic peptide (BNP) levels, increased pulmonary capillary wedge pressure, and progression of HF.[3−8] Earlier studies investigating the influence of CSA on mortality in patients with HF, however, have yielded contradictory results.[13−26] In addition, most studies were limited by small patient populations, retrospective study designs, few end points during follow-up, no uniform use of ventilation therapy, and polygraphy instead of polysomnography as criterion standard to diagnose CSA. Therefore, we performed a prospective observational study with the use of polysomnography to determine whether untreated moderate CSA or severe CSA is associated with total mortality or need for heart transplantation compared with no CSA or mild CSA in a large patient population with stable HF.

Methods

Patients

From August 2007 to June 2011, we prospectively screened 300 adult patients for sleep-disordered breathing with the use of polysomnography at the department of internal medicine and cardiology in our hospital who fulfilled the following inclusion criteria: systolic HF due to ischemic or nonischemic cardiomyopathy, New York Heart Association (NYHA) class I−III in a stable condition with unchanged medical HF treatment for ≥1 month, and

From the [1]Department of Cardiology, University Hospital of Marburg and Gießen, Marburg, Germany; [2]Institute for Medical Biometry and Epidemiology, Philipps-University Marburg, Marburg, Germany and [3]Sleep Disorder Unit of the Department of Pneumology, University Hospital of Marburg and Gießen, Marburg, Germany

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Reprint requests: Wolfram Grimm, MD, Department of Cardiology, Philipps-University Marburg, Baldingerstraße, 35033 Marburg, Germany. Tel: +49-6421-586-9748; Fax: +49-6421-586-8954. E-mail: grimmw@med.uni-marburg.de

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left ventricular (LV) ejection fraction ≤50% according to echocardiography. The LV ejection fraction cutoff of ≤50% according to echocardiography to define systolic LV dysfunction was based on the recommendations of the European Echocardiography Association[27] and European Society of Cardiology guidelines for diagnosis and treatment of HF.[28] Patients were excluded from study enrollment if they had ≥1 of the following conditions: history of sleep-disordered breathing or previous polygraphy or polysomnography for suspected sleep-disordered breathing, advanced kidney disease with an estimated glomerular filtration rate (eGFR) < 15 mL min^{-1} 1.73 m^{-2} or hemodialysis, advanced liver disease, including liver cirrhosis Child class B or C, advanced pulmonary disease, including pulmonary fibrosis and chronic obstructive lung disease Gold stage 3 or 4, pregnancy, malignancies, and current or past alcohol or drug abuse. In addition, 33 of 300 patients who underwent baseline polysomnography were subsequently excluded because of OSA despite a negative patient history for OSA, insufficient sleep studies, or withdrawal of consent, as summarized in Figure 1. The study protocol was reviewed and approved by the Ethics Committee of the University of Marburg. Patients were screened for study participation primarily at the department of Cardiology of the Hospital of the University of Marburg. Written informed consent was obtained from each of the study patients who met the inclusion criteria mentioned above at the time of study enrollment after echocardiography had confirmed that LV ejection fraction was ≤50%. Polysomnography was performed after written informed consent had been obtained within 1 week after baseline echocardiography including LV ejection fraction measurement as described below.

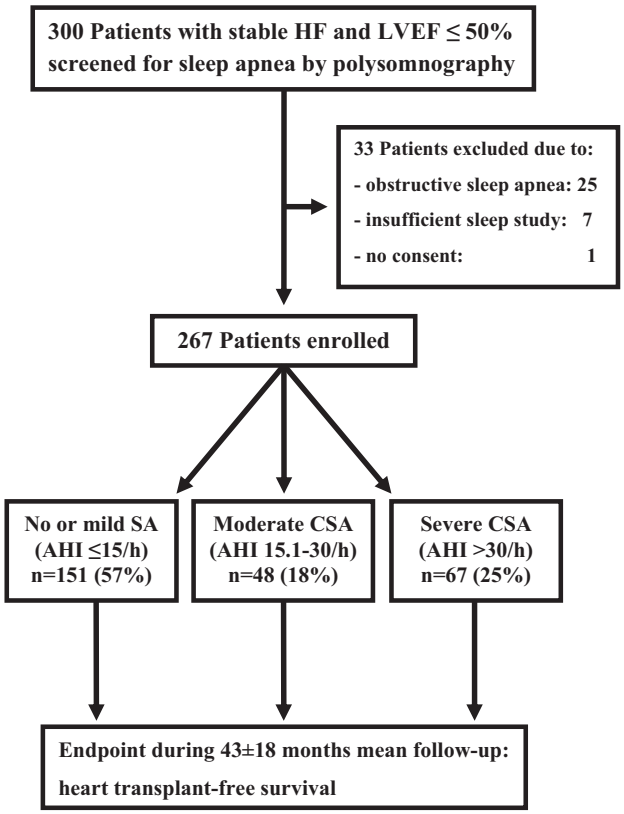

Fig. 1. Study profile. AHI, apnea/hypopnea index; CSA, central sleep apnea; HF, heart failure; LVEF, left ventricular ejection fraction.

Polysomnography

Unattended overnight cardiorespiratory polysomnography was performed during 1 night with the use of Somnocheck 2 R&K instruments (Weinmann, Hamburg, Germany) and analyzed according to the recommendations of the American Academy of Sleep Medicine.[29] Somnocheck 2 R&K is a 24-channel device to perform full polysomnography. The device includes flow measurement with the use of a nasal cannula and a respiratory flow sensor, a thorax and abdominal piezo belt to measure thoracoabdominal excursions, finger sensors for continuous measurement of oxygen saturation, blood pressure measurement, and position sensor, electrocardiograph electrodes, electromyograph electrodes at chin and leg, 3 electroencephalograph electrodes, and 2 electrooculograph electrodes. All measurements of the Somnocheck 2 R&K device were stored on an integrated, interchangeable compact flash card. The Somnocheck 2 R&K device was applied by sleep technicians in the evening before polysomnography, and the patients stayed overnight unattended in the hospital in a regular bedroom outside of the sleep laboratory. In the next morning, the Somnocheck 2 R&K device was removed by a sleep technician, and all data for a complete polysomnography were retrieved from the integrated compact flash memory card, visualized, and analyzed with the use of special software (Somnolab version 2.01 and Somnoligica version 3.3.1). All polysomnography recordings were scored by a sleep technician and with the sleep technician's scoring being overread by a sleep medicine physician, both of whom were unaware of the patients' clinical characteristics. The sleep technician who applied the Somnocheck 2 R&K device also routinely assessed daytime sleepiness with the use of the Epworth Sleepiness Scale in conjunction with polysomnography. Standard definitions were used for sleep-related disordered breathing.[29,30] An apnea was defined as cessation of inspiratory airflow >10 s. The number of apneas and hypopneas per hour of sleep is referred to as apnea/hypopnea index (AHI). No or mild sleep apnea was diagnosed in the presence of an AHI ≤15/h. An AHI >15/h but ≤30/h defined the presence of moderate sleep apnea. Severe sleep apnea was diagnosed in the presence of an AHI >30/h.[30] CSA was defined as the absence of rib cage and abdominal excursions with absence of airflow. OSA was defined as the absence of airflow in the presence of rib cage and abdominal excursions. Similarly to most previous studies, CSA was diagnosed when the number of central apneas was >50% of all apnea events.[1,2,6,8,9,11,23,30]

Echocardiography

Two-dimensional echocardiographic examinations were performed in all patients with the use of a Vingmed Vivid Seven machine (General Electronics Medical Systems, Solingen, Germany) to determine left atrial diameter, LV ejection fraction, and LV size. LV ejection fraction was measured in the apical 4-chamber view and orthogonal 2-chamber view by means of the disc summation method (modified Simpson rule algorithm). Echocardiography was performed within 1 week of study enrollment after the patient had been stable without change in HF medication for ≥4 weeks.

Kidney Function

Kidney function was assessed at study entry within 1 week of polysomnography by means of the eGFR with the use of the Modification of Diet in Renal Disease formula.[31,32]

Follow-up

Follow-up started at the time of polysomnography and ended in December 2013. The study protocol required follow-up information of all patients in intervals of ≤12 months. The majority of patients with stable HF in NYHA functional class I or II were followed regularly in 12-month intervals in our cardiology outpatient clinic. Patients who did not use our cardiology outpatient department for follow-up visits were followed by telephone contact with the patient and their referring physician. Most patients with more advanced HF in NYHA functional class III, as well as patients with implantable cardioverter-defibrillators (ICDs) or cardiac resynchronization therapy devices were followed in 6-month intervals. Patients with symptoms indicating worsening HF or symptomatic arrhythmias were asked to come as soon as possible for additional follow-up visits. Follow-up was completed in 255 of 267 study patients (96%). The remaining 12 patients (4%), who were lost during follow-up because they moved to an unknown new address, were censored at the time of their last follow-up. Predefined end point of follow-up was all-cause mortality or heart transplantation. Initiation of ventilation therapy was discouraged by the study protocol because we sought to investigate the prognostic significance of CSA in untreated patients and because ventilation therapy has not been proven to improve survival in HF patients with CSA.[33] Owing to the attending physician's wish or the patient's wish, however, 8 of 267 study patients (3%) received either continuous positive airway pressure ventilation[33] or adaptive servoventilation[34] during follow-up. These 8 patients were not censored or retrospectively excluded from study participation.

Statistical Analysis

Baseline clinical characteristics between patients with no or mild CSA (AHI <15/h), moderate CSA (AHI 15−30/h), and severe CSA (AHI >30/h) were compared with the use of the Jonckheere-Trepsta trend test for continuous variables, the Cochran-Armitage trend test for nominal variables, and the Kendall tau-b test for ordinal variables. Univariate and multivariate Cox regression analyses were used to evaluate the association between baseline variables as listed in Table 1 and heart transplant−free survival as predefined outcome measure. The final Cox regression model was built by a stepwise procedure, with a cutoff level of 0.20 for entry into the model. In addition, multivariate Cox regression analysis was repeated including severe CSA as a dichotomized variable with an AHI cutoff >30/h as suggested by several earlier studies.[16,24,32] Event-free survival probabilities were estimated with the use of the Kaplan-Meier method. Results are expressed as mean ± SD unless specified otherwise. All probability values reported are 2 sided, and a probability value of $P < .05$ was considered to indicate statistical significance. R software

Table 1. Transplant-Free Survival

Baseline Characteristics	All Patients (n = 267)	Survival (n = 196)	Death/HT (n = 71)	*P* Value, Univ	*P* Value, Multiv	HR (95% CI)
Age, y	60 ± 14	58 ± 14	67 ± 13	<.001	.005	1.18 (1.05−1.31)*
Male sex, n (%)	201 (75)	138 (70)	63 (89)	.002	.005	2.88 (1.37−6.06)
Body mass index, kg/m^2	28 ± 5	28 ± 5	27 ± 6	.714		
Diabetes mellitus, n (%)	75 (28)	48 (24)	27 (38)	.043		
Chronic kidney disease, n (%)	84 (31)	44 (22)	40 (56)	<.001	.004	2.18 (1.29−3.67)
Atrial fibrillation, n (%)	70 (26)	43 (22)	27 (38)	.007		
Left bundle branch block, n (%)	50 (19)	40 (20)	10 (14)	.224	.187	0.64 (0.32−1.25)
LV ejection fraction, %	34 ± 10	35 ± 10	30 ± 10	<.001	.007	1.19 (1.05−1.36)†
LV end-diastolic diameter, mm	61 ± 9	61 ± 9	62 ± 9	.246		
Ischemic cardiomyopathy, n (%)	124 (46)	79 (40)	45 (63)	.001		
Nonischemic cardiomyopathy, n (%)	143 (54)	117 (60)	26 (37)			
B-Type natriuretic peptide (pg/ml)	684 ± 851	486 ± 623	1,229 ± 1,123	<.001		
NYHA heart failure functional class, n (%)				.152		
I	39 (15)	33 (17)	6 (8)			
II	99 (37)	73 (37)	26 (37)			
III	129 (48)	90 (46)	39 (55)			
Implantable cardioverter-defibrillator (ICD), n (%)				.537		
Single- or dual-chamber ICD	86 (32)	60 (31)	26 (37)			
CRT-ICD	34 (13)	23 (12)	11 (16)			
Medications, n (%)					.149	1.77 (0.83−3.80)
ACE inhibitors or ARBs	177 (66)	134 (68)	43 (61)	.210		
Diuretics	194 (73)	131 (67)	63 (89)	<.001		
Aldosterone antagonists	105 (39)	80 (41)	25 (35)	.521		
β-Blockers	211 (79)	159 (81)	52 (73)	.289		
Polysomnography results, n (%)						
AHI, n/h	19.1 ± 18.9	18.2 ± 18.3	21.5 ± 20.4	.213		
No or mild SA (AHI ≤15/h)	151 (57)	114 (58)	37 (52)	.250		
Moderate CSA (AHI 15.1−30/h)	49 (18)	38 (19)	11 (16)			
Severe CSA (AHI >30/h)	67 (25)	44 (22)	23 (32)			
Ventilation therapy, n (%)	8 (3)	7 (4)	1 (1)	.388		

HT, heart transplant; Univ, univariate; Multiv, multivatiate; HR, hazard ratio; CI, confidence interval; LV, left ventricular; NYHA, New York Heart Association; CRT, cardiac resynchronization therapy; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AHI, apnea/hypopnea index; SA, sleep apnea; CSA, central sleep apnea.

*Per 5-year increase in age.

†Per 5% decrease in LV ejection fraction.

version 3.02 (www.R-project.org) with the Survival package was used for all statistical analyses.

Results

Characteristics of 267 Study Patients

The clinical characteristics of the 267 study patients and the results of polysomnography are summarized in Tables 2 and 3. No or mild CSA (AHI <15/h) was found in 151 patients (57%), 49 patients (18%) had moderate CSA (AHI 15−30/h), and 67 patients (25%) had severe CSA (AHI >30/h). Mean age was 60 ± 14 years, and mean LV ejection fraction was 34 ± 10%. Chronic kidney disease of stage ≥3 was diagnosed in 84 patients (32%), with 2 eGFR values <60 mL min^{-1} 1.73 m^{-2} with an interval of ≥3 months. Univariate comparison of patients with no or mild CSA, moderate CSA, and severe CSA demonstrated a significant association between CSA and age, male sex, body mass index, diabetes, chronic kidney disease, LV end-diastolic diameter, BNP, and the use of single- or dual-chamber ICDs. In addition, LV ejection fraction tended to be lower and the prevalence of atrial fibrillation tended to be higher in patients with versus without severe CSA (Table 2). Polysomnography results are summarized in Table 3. Daytime sleepiness assessed with the use of the Epworth Sleepiness Scale was similar in patients with and without CSA. Patients with severe CSA had more arousals and spent less time in sleep stages 3 and 4 and rapid eye movement sleep compared with patients without severe CSA. In addition, the time with oxygen saturation <90% was significantly longer in patients with severe CSA.

Predictors of Heart Transplant−Free Survival

During 43 ± 18 months' mean follow-up, 67 patients (25%) died and 4 patients (1%) underwent heart transplantation (Table 1). On univariate analysis, transplant-free survival was associated with younger age, female sex, absence of diabetes, chronic kidney disease, and atrial fibrillation, LV ejection fraction, nonischemic versus ischemic cardiomyopathy, BNP, and use of diuretics. Multivariate Cox analysis identified age, male sex, chronic kidney disease, and LV ejection fraction, but not moderate CSA or severe CSA as predictors of heart transplant−free survival (Table 1; Fig. 2). The Kaplan-Meier estimates for transplant-free survival of 267 HF patients dichotomized at AHI cutoffs of 15/h and 30/h are shown in Figure 3. Although the log-rank test showed a trend toward decreased survival for patients with severe CSA (AHI >30/h; P = .098), multivariate Cox regression analysis revealed no significant difference in transplant-free survival between patients with and without severe CSA after adjustment for potential confounding factors (hazard ratio 0.85, 95% confidence interval 0.50−1.44; P = .54).

Discussion

This prospective study performed polysomnography in 267 patients with HF and compared heart transplant−free survival between patients with no or mild CSA, moderate CSA, and severe CSA. Multivariate Cox analysis identified age, male sex, chronic kidney disease, and LV ejection

Table 2. Presenting Characteristics According to Sleep Study Results

Baseline Characteristics	All Patients	No or Mild CSA	Moderate CSA	Severe CSA	*P* Value
Patients, n (%)	267 (100)	151 (57)	49 (18)	67 (25)	
Age, y	60 ± 14	58 ± 15	62 ± 14	65 ± 11	<.001
Men, n (%)	201 (75)	101 (67)	42 (86)	58 (87)	.001
Body mass index, kg/m^2	28 ± 5	27 ± 5	28 ± 5	29 ± 5	.037
Diabetes mellitus, n (%)	75 (28)	33 (22)	16 (33)	26 (39)	.008
Chronic kidney disease, n (%)	84 (32)	41 (27)	15 (31)	28 (42)	.037
Atrial fibrillation, n (%)	70 (26)	38 (25)	5 (10)	27 (40)	.070
Left bundle branch block, n (%)	50 (19)	29 (19)	11 (22)	10 (15)	.545
LV ejection fraction, %	34 ± 10	35 ± 10	34 ± 9	32 ± 10	.064
LV end-diastolic diameter, mm	61 ± 9	60 ± 8	62 ± 9	64 ± 9	.001
Ischemic cardiomyopathy, n (%)	124 (46)	64 (42)	22 (45)	38 (57)	.057
Nonischemic cardiomyopathy, n (%)	143 (54)	87 (58)	27 (55)	29 (43)	
B-Type natriuretic peptide (pg/ml)*	685 ± 852	550 ± 705	647 ± 872	1,015 ± 1,041	<.001
NYHA heart failure functional class, n (%)					.240
I	39 (15)	25 (17)	8 (16)	6 (9)	
II	99 (37)	56 (37)	18 (37)	25 (37)	
III	129 (48)	70 (46)	23 (47)	36 (54)	
Implantable cardioverter-defibrillator, n (%)					.047
Single- or dual chamber ICD	86 (32)	37 (25)	17 (35)	32 (48)	
CRT-ICD	34 (13)	20 (13)	9 (18)	5 (7)	
Medications, n (%)					
ACE inhibitors or ARBs	177 (66)	99 (66)	36 (74)	42 (59)	.841
Diuretics	194 (73)	106 (70)	37 (76)	51 (76)	.328
Aldosterone antagonists	105 (39)	56 (37)	22 (45)	27 (40)	.551
β-Blockers	211 (79)	120 (80)	40 (82)	51 (76)	.642

Abbreviations as in Table 1.
*Available in 251 patients.

Table 3. Polysomnography Results

	All Patients	No or Mild CSA	Moderate CSA	Severe CSA	*P* Value
Patients, n (%)	267 (100)	151 (57)	49 (18)	67 (25)	
AHI, n/h	19.1 ± 18.9	5.6 ± 4.4	21.7 ± 4.6	47.4 ± 12.1	<.001
Epworth Sleepiness Scale	6.3 ± 3.6	6.2 ± 3.6	6.2 ± 4.2	6.7 ± 3.5	.407
Central apnea index, n/h	14.8 ± 17.4	3.0 ± 3.7	16.6 ± 7.2	40 ± 14	<.001
Obstructive apnea index, n/h	0.6 ± 1.9	0.4 ± 1.4	0.6 ± 1.6	1.1 ± 2.8	.470
Mixed apnea index, n/h	0.9 ± 3.8	0.1 ± 0.3	0.6 ± 1.9	3.1 ± 6.9	<.001
Hypopnea index, n/h	2.7 ± 4.9	2.1 ± 2.9	3.9 ± 4.8	3.2 ± 7.6	.131
Total in bed time, min	512 ± 43	519 ± 32	497 ± 66	506 ± 42	.010
Total sleep time (TST), min	304 ± 96	311 ± 94	298 ± 99	293 ± 99	.115
Arousals, n/h	15 ± 9	12 ± 7	15 ± 9	20 ± 12	<.001
Sleep stage 1, % TST	20 ± 17	17 ± 15	20 ± 17	25 ± 20	.003
Sleep stage 2, % TST	47 ± 15	47 ± 14	46 ± 15	49 ± 17	.289
Sleep stages 3 and 4, % TST	19 ± 13	20 ± 12	19 ± 10	14 ± 10	<.001
Rapid eye movement, % TST	15 ± 8	16 ± 9	15 ± 6	13 ± 8	.04
Sleep efficiency, %	60 ± 18	60 ± 18	60 ± 19	58 ± 19	.445
Sleep latency, min	45 ± 51	52 ± 58	40 ± 44	31 ± 35	.005
Mean O_2 saturation, %	94.7 ± 3.1	95.2 ± 3.1	94.3 ± 3.3	93.9 ± 2.8	<.001
O_2 saturation <90%, % TST	20 ± 33	17 ± 27	21 ± 43	28 ± 30	<.001

CSA, central sleep apnea.

fraction, but not moderate CSA or severe CSA as predictors of transplant-free survival.

Prevalence of CSA in Heart Failure

Several earlier studies reported a high prevalence of CSA in patients with HF, ranging from 21% to 82%.[1–26] This wide range of CSA frequency in HF patients may be explained by a number of variables, including HF severity and etiology, age, sex, and HF medication. In addition, AHI cutoff values used to define CSA in earlier studies varied considerably from 5/h[3,18,20–22,26] to 30/h.[16,30] With the use of an AHI cutoff >15/h, polysomnography revealed a CSA prevalence of 43% in our study, similar to 40% in the study by Javaheri et al,[1] 44% in the study by Sin et al,[17] and 53% in the study by Vazir et al.[7] Consistent with the findings of our study, both CSA prevalence and CSA severity have been associated in HF patients with older age, male sex, and atrial fibrillation in addition to HF severity with increased neurohumoral activation, higher BNP levels, increased pulmonary capillary wedge pressure, and lower LV ejection fraction.[1–8,10,11] Therefore, unlike OSA, CSA likely represents a consequence of HF, indicating the need to optimize HF therapy.

CSA and Transplant-Free Survival

To the best of our knowledge, this is the first prospective study to assess the prognostic significance of predominantly untreated CSA in >200 HF patients, which revealed advanced age, male sex, chronic kidney disease, and decreased LV ejection fraction, but not CSA, as independent predictors of mortality or heart transplantation. Earlier studies investigating the prognostic significance of CSA yielded contradictory results.[13–26] Eight earlier studies[13,16,17,19,20,23,25,26] reported a higher mortality in patients with CSA, although 6 others failed to demonstrate an increased mortality in patients with CSA.[14,15,18,21,22,24] Most of those studies had ≥1 of the following limitations: small patient populations with few end points during follow-up, retrospective study design, use of polygraphy rather than polysomnography as criterion standard to detect CSA, no uniform use of ventilation, and lack of multivariate analysis to adjust for confounding variables. The 1st small study designed to specifically determine the impact of CSA on mortality in HF was reported by Hanly et al in 1996.[13] Hanly et al[13] performed polysomnography in 16 HF patients and found a significantly higher 3-year mortality of 56% in 8 patients with CSA compared with 11% in 8 patients without CSA. The results of subsequent studies with <100 patients per study, however, were divergent.[14–18,20] Consistently with our findings, Roebuck et al[18] observed similar mortality rates for patients with and without CSA during 52 months' median follow-up in 78 HF patients who had been referred for transplantation consideration. Conversely, Javaheri et al[20] found a significantly decreased median survival time in 88 HF patients in the presence of higher AHI than of lower AHI across all AHI cutoff points of 5/h, 10/h, 15/h, 20h, 25/h, and 30h. Multivariate analysis in the study by Javaheri et al[20] revealed that severe right ventricular systolic dysfunction and low diastolic blood pressure independently correlated with survival in addition to CSA.

To date, only 3 earlier studies have prospectively investigated the prognostic significance of untreated CSA in >100 HF patients.[19,21,24] The 1st study, by Corrà et al[19] enrolled 133 HF patients with a mean LV ejection fraction of 23% and observed 31 deaths (23%) during 39 months' mean follow-up. Corrà et al[19] found an AHI >30/h to be the best cutoff value for predicting mortality with the use of receiver operating characteristic curves at regular intervals. In contrast to our study, Corrà et al[19] found a higher total mortality of 39% in patients with AHI >30/h compared with only 9% in patients with AHI ≤30/h, which remained significant after adjustment for potential

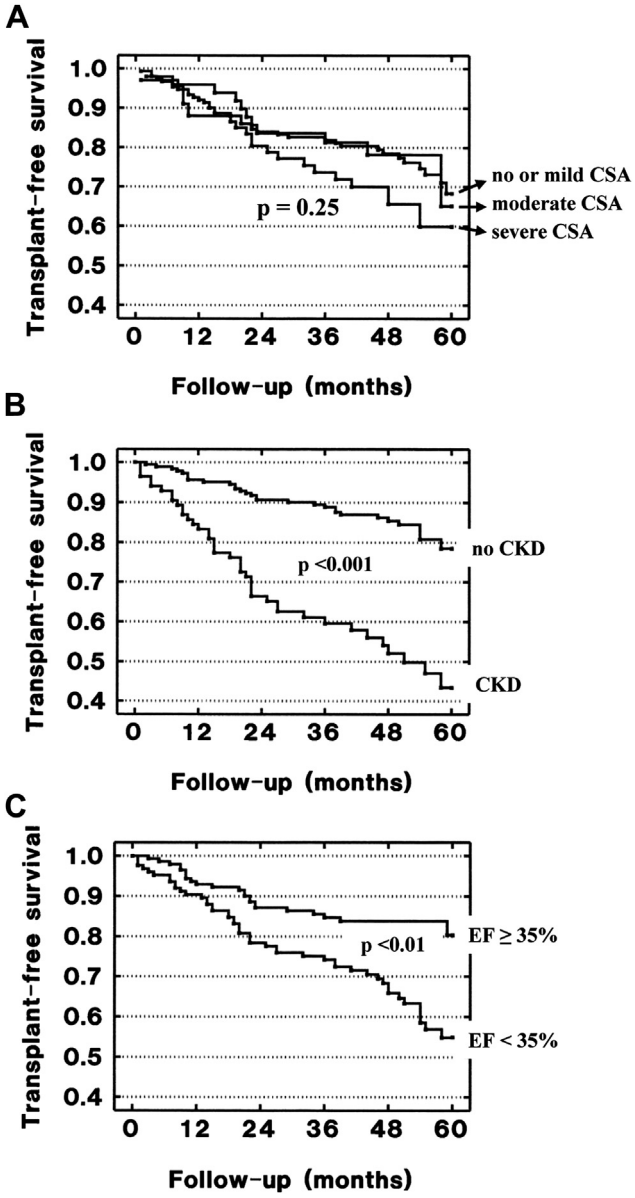

Fig. 2. Kaplan-Meier estimates for transplant-free survival of 267 study patients with HF stratified for (A) no or mild central sleep apnea (CSA; apnea/hypopnea index [AHI] ≤15/h), moderate CSA (AHI 15−30/h, and severe CSA (AHI >30/h); (B) chronic kidney disease (CKD) defined as estimated glomerular filtration rate <60 mL min^{-1} 1.73 m^{-2}; and (C) left ventricular ejection fraction (EF) dichotomized at the median EF of 35%.

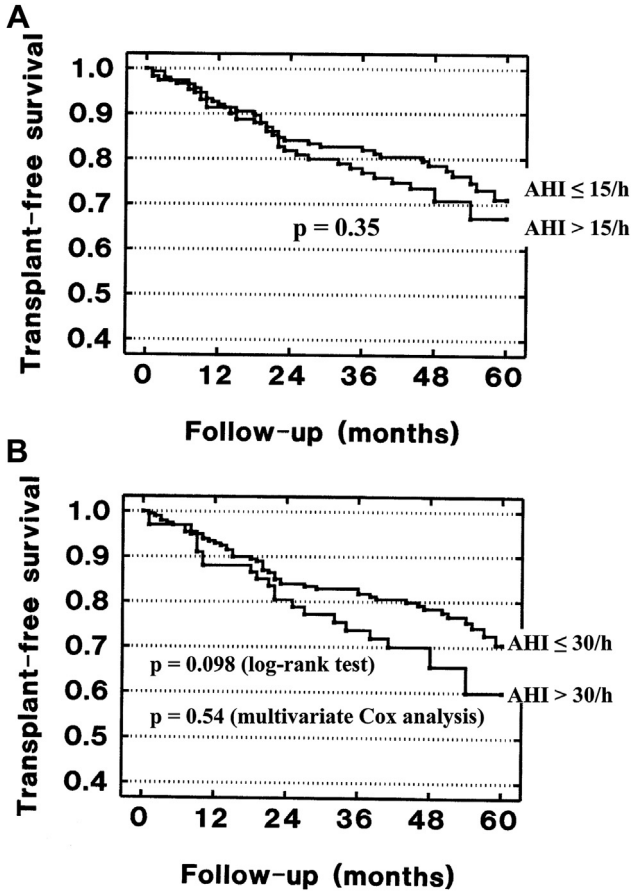

Fig. 3. Kaplan-Meier estimates for transplant-free survival of 267 study patients with HF, dichotomized at an AHI cutoff of (A) 15/h and (B) 30/h. Although the log-rank test showed a trend toward decreased survival for patients with severe CSA with an AHI >30/h (P = .098), multivariate Cox regression analysis revealed no significant difference in transplant-free survival between patients with versus without severe CSA using an AHI cutoff of 30/h after adjustment for potential confounding factors, as summarized in Table 3 (hazard ratio 0.85, 95% confidence interval 0.50−1.44; P = .54).

confounding comorbidities by multivariate analysis. Repeated multivariate analysis of potential predictors of transplant-free survival in our study, including severe CSA as a dichotomized variable with AHI >30/h as in the study by Corrà et al,[19] did not change the negative results of our study regarding the prognostic impact of severe CSA (Fig. 3B). Whether the inconsistency of the study results between Corrà et al[19] and our study are due to differences in patient population, with a significantly lower mean LVEF of 23% in the former study[19] compared with 34% in our study, remains unknown. The 2nd study, by Luo et al,[21] assessed the prognostic impact of sleep apnea in 124 selected HF patients who had no sleep apnea or who had sleep apnea but refused or discontinued recommended positive-pressure ventilation after patients with sleep apnea who accepted positive-pressure ventilation had been excluded. Consistently with the findings of our study, Luo et al[21] did not find untreated CSA or CSA severity to predict survival after adjustment for confounding factors according to multivariate Cox analysis. In contrast to the majority of earlier studies, including our study, Luo et al[21] used a low AHI threshold of ≥5/h to define CSA without reporting outcome in subgroups with higher AHI cutoffs. The 3rd study, by Khayat et al,[24] was designed to determine whether CSA using an AHI cutoff >15/h was a predictor of cardiac readmission within 6 months' follow-up in a large cohort of 784 consecutive hospitalized HF patients. As a result, Khayat et al[24] found CSA to be an important independent predictor for 6-month cardiac

readmissions in addition to baseline LV ejection fraction, which was significantly lower in patients with versus without CSA (22% vs 30%, respectively). Despite this significant difference in baseline LV ejection fraction, Khayat et al[24] did not observe differences in mortality between patients with versus without CSA (16% vs 15%, respectively). These findings are consistent with the results of our study including CSA as a dichotomized variable using the same AHI cutoff >15/h as Khayat et al[24] (Fig. 3A). Mortality data of the study by Khayat et al,[24] however, are limited by the short mean follow-up duration of 6 months.

Study Limitations

Our study has several limitations. Owing to limited research capacity in our sleep laboratory, we were unable to enroll consecutive HF patients presenting at our hospital. Instead, we enrolled the 1st 1 or 2 HF patients presenting at a given day at the department of cardiology in our hospital who fulfilled the inclusion criteria because the study protocol required complete polysomnography, which is the current criterion standard to detect and quantify sleep-disordered breathing[29,34] rather than simple polygraphy in all patients. In addition, 8 of 267 patients (3%) received ventilation therapy during follow-up according to decision of the patient and their attending physician, although the use of ventilation therapy was discouraged at study enrollment because we sought to investigate the prognostic significance of untreated CSA in patients with stable HF. We adjusted for ventilation therapy during follow-up as a potential confounding factor for transplant-free survival with the use of multivariate analysis.

Conclusion

In patients with stable HF, moderate CSA and severe CSA do not appear to be associated with an increased risk of death or need for heart transplantation after adjustment for confounding factors. In contrast to moderate CSA or severe CSA, chronic kidney disease is an important independent predictor of total mortality or heart transplantation in addition to advanced age, male sex, and decreased LV ejection fraction. Our findings support the hypothesis that CSA is merely a marker for HF severity rather than a risk factor for an adverse prognosis in HF patients.

Disclosures

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